Tetrahedron Vol. 41, No 15, pp. 3141 to 3146, 1985
Printed in Great Britain.

0040-4020/85 $3.00 + .00

ISOLATION AND STRUCTURAL ELUCIDATION OF HELIANGOLIDIN, A NEW SESQUITERPENE LACTONE FROM ARTEMISIA CANARIENSIS.

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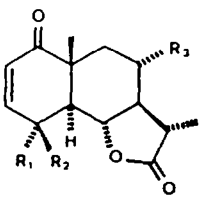
(*Received in UK* 18 *April* 1985)

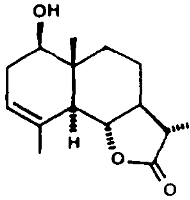
Abstract - A new heliangolide has been isolated from aerial parts of Artemisia canariensis, and identified as (6E,10Z)(3S,3aR,4S,11aR)-3a,5,8,11a-tetrahydro-4-acetoxy-3,6,10-trimethyl-2,9(3H,4H)-cyclodeca[b]furandione. The structural elucidation of the new compound, named heliangolidin, was carried out by spectral means (MS, IR, ^1H and ^{13}C NMR, and two dimensional ^1H-^{13}C chemical shift correlations) and X-ray diffraction analysis.

In the aerial parts of Artemisia canariensis Lees (Compositae), an endemic plant of the Canary Islands, we had previously found six eudesmanolides[1,2] : vulgarin (1), tabarin (2), acetyltabarin (3), 4-epivulgarin (4), 11,13-dihydrosantamarin (5) and 11,13-dihydroreynosin (6).

In the present communication, we report on the isolation from the same plant of heliangolidin (7), a new sesquiterpene lactone with a germacradiene structure of the heliangolide class. This structure has been elucidated by spectral means (MS, IR, ^1H and ^{13}C NMR, and two dimensional ^1H-^{13}C chemical shift correlations) and X-ray diffraction analysis.



1 $R_1 = OH;\ R_2 = CH_3;\ R_3 = H$
2 $R_1 = R_3 = OH;\ R_2 = CH_3$
3 $R_1 = OH;\ R_2 = CH_3;\ R_3 = OAc$
4 $R_1 = CH_3;\ R_2 = OH;\ R_3 = H$



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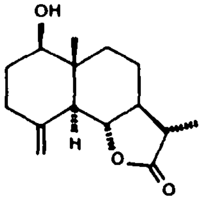

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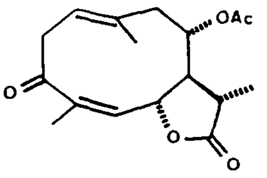


7

The new compound, m.p. 187-189°C, $[\alpha]_D = +216.5°$, gave satisfactory elemental analysis for a $C_{17}H_{22}O_5$ formula, in agreement with the molecular ion at m/z 306 exhibited by its mass spectrum. The presence of an acetate group was indicated by base peak at m/z 43, M-60 fragment at m/z 246 and by IR absorption at 1735 cm^{-1}. Two other carbonyl absorptions appeared at 1765 and 1695 cm^{-1} attributable to a γ-lactone and an α,β-unsaturated carbonyl groups respectively.

As shown in Table 1, the ^1H NMR spectrum revealed the occurrence of four methyl absorptions, namely, two vinyl methyls at δ 1.73 (singlet) and δ 1.86 (doublet, J=1.6 Hz), a methyl α to the lactone carbonyl group at δ 1.37 (doublet, J=7.7 Hz) and the methyl of the acetate moiety at δ 2.04 (singlet). Two vinyl proton absorptions appeared at δ 5.17 (doublet of doublets, J=10.4 and

1.6 Hz) and 5.36 (triplet, J=8.5 Hz). The presence of two protons linked to oxygen-bearing carbons was inferred from resonance signals at δ 4.10 (doublet of doublets, J=10.4 and 2.5 Hz) and 4.86 (triplet of doublets, J=10.8 and 3.7 Hz).

Irradiation of the doublet of quadruplets at δ 5.17, attributable to H-5, brings about the simultaneous collapse of the doublet of doublets at δ 4.10 to a doublet (J=2.5) and that of the vinyl methyl doublet at δ 1.86 to a singlet. Conversely, irradiation of the lactonic proton H-6 at δ 4.10 transformed the H-5 signal into a broad singlet and simplified the complex absorption at δ 2.0-2.3 making it possible to assign the H-7 resonance signal as the expected doublet of doublets of doublets (J=10.8, 3.6 and 2.5 Hz). Likewise, irradiation at this last resonance introduced notable changes in the spectrum: H-6 was reduced to a doublet (J=10.4), the H-8 triplet of doublets at δ 4.86 collapsed into a broad doublet due to the simultaneous partial saturation of H-9α, while the H-11 quadruplet of doublets at δ 2.50 was converted into a quartet. This signal was also identified by irradiation of the corresponding H-13 absorption, a doublet (J=3.6) being then observed.

A double resonance experiment at the frequency of H-8 converted the doublet of doublets centered at δ 2.63 into a doublet (J=11.9), and also simplified the complex region of the spectrum between δ 2.0-2.3: the H-7 multiplet collapsed into a broad signal and the doublet of doublets at 2.22 into a doublet (J=11.9). These results indicated that H-8 was adjacent to a methylene group (H-9α and H-9β). Likewise, irradiation at the H-9β resonance signal transformed H-8 into a triplet (J=10.8), but into a broad signal when H-9α was irradiated. The aspect of the signals of this methylene group indicated that the contiguous C-10 should be a quaternary carbon atom.

On the other hand, the small value of $J_{6,7}$ (2.5 Hz) suggested that this lactone must be a trans $\Delta^{1,10}$,cis $\Delta^{4,5}$-germacranolide (heliangolide) with a trans configuration in the fused γ-lactone ring[3-6]. The analysis of the coupling constants $J_{7,8}$ and $J_{8,9}$ revealed that the acetoxy group at C-8 must be α-oriented.

Moreover, compound 7 exhibited the partial structural arrangement $-CH_2-CH=C(CH_3)-$ which accounted for the vinyl and vinyl methyl absorptions above mentioned. This moiety was disclosed by a further double resonance experiment. Irradiation of H-1 signal at δ 5.36 transformed the methylene doublet at δ 3.13 into a broad singlet indicating that this methylene must be joined to a quaternary carbon or carbonyl group. All the combined portions, taking into account the isoprene rule, were in agreement with structure 7.

Furthermore, as shown in Table 2, the ^{13}C NMR spectrum confirmed the above structure. The presence of three carbonyl groups was inferred from absorptions at δ 201.34 (α,β-unsaturated carbonyl), 178.42 (lactone carbonyl) and 169.87 (acetate). Likewise, the occurrence of four vinyl carbons was deduced from resonance signals at δ 140.7 and 136.8, attributable to quaternary carbons C-4 and C-10 and at δ 119.4 and 125.5, assigned to tertiary carbons C-1 and C-5 respectively. The absorptions of tertiary carbon atoms C-6 and C-8, joined to oxygen atoms, appeared at δ 78.44 and 72.55, whereas remaining tertiary carbon atoms C-7 and C-11 exhibited resonance signals at δ 53.67 and 38.13, respectively, and secondary carbons C-2 and C-9 presented their corresponding signals at δ 41.41 and 46.6. It is worth of note that absorption of C-11 atom showed a greater upfield shift than that of C-7, due to the presence in γ-position of two oxygenated substituents at C-6 and C-8[7]. Likewise, signal of C-2 was shifted upfield when compared to that of C-9, due to the effect of methyl groups at C-4 and C-10[8]. The assignment of some of these signals cannot be made unambiguously and to obviate this problem, as shown in Fig. 2, a two dimension spectrum with ^{1}H-^{13}C correlations was carried out.

An X-ray analysis of heliangolidin was undertaken to assure the stereochemical assignment and to shed further light on the various conformations assumed. Fig. 3 shows the stereoscopic view of the molecule conformation and the atom numbering of the crystal structure. All pertinent bond distances and angles are given in Tables 3 and 4, respectively[†].

[†] Calculated and observed structure factors, anisotropic thermal parameters and hydrogen atom coordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road,Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

TABLE 1. ^{1}HNMR spectrum of Heliangolidin (200 MHz, δ, $CDCl_3$, J(Hz))

H- 1	5.36	t	$J_{1,2}= 8.5$
H- 2	3.13	d	$J_{2,1}= 8.5$
H- 5	5.17	dq	$J_{5,6}=10.4$; $J_{5,15}= 1.6$
H- 6	4.10	dd	$J_{6,5}=10.4$; $J_{6,7}= 2.5$
H- 7	2.13	m	
H- 8	4.86	td	$J_{8,7}=J_{8,9\alpha}=10.8$; $J_{8,9\beta}=3.7$
H- 9α	2.22	dd	$J_{9\alpha,9\beta}=11.9$; $J_{9\alpha,8}=10.8$
H- 9β	2.63	dd	$J_{9\beta,9\alpha}=11.9$; $J_{9\beta,8}= 3.7$
H-11	2.50	qd	$J_{11,13}= 7.7$; $J_{11,7}= 3.6$
H-13	1.37	d	$J_{13,11}= 7.7$
H-14	1.73	s	
H-15	1.86	d	$J_{15,5} = 1.6$
CH_3COO	2.04	s	

TABLE 2. ^{13}CNMR spectrum of Heliangolidin (50.32 MHz, δ, $CDCl_3$)

C-1	119.40	C-10	136.80
C-2	41.41	C-11	38.13
C-3	201.34	C-12	178.42
C-4	140.70	C-13	18.90
C-5	125.50	C-14	16.81
C-6	78.44	C-15	19.70
C-7	53.67	$CH_3\underline{C}OO$	169.87
C-8	72.55	$\underline{C}H_3COO$	21.09
C-9	46.60		

TABLE 3. Bond Distances (Å) for Heliangolidin

Atom 1	Atom 2	Distance
C(1)	C(2)	1.488(6)
C(2)	C(3)	1.526(6)
C(3)	O(3)	1.203(5)
C(3)	C(4)	1.507(7)
C(4)	C(15)	1.531(6)
C(4)	C(5)	1.335(6)
C(5)	C(6)	1.516(5)
C(6)	O(6)	1.465(5)
O(6)	C(12)	1.338(5)
C(12)	O(12)	1.206(5)
C(12)	C(11)	1.500(6)
C(11)	C(13)	1.507(7)
C(11)	C(7)	1.541(5)
C(7)	C(6)	1.566(5)
C(7)	C(8)	1.529(5)
C(8)	C(9)	1.538(5)
C(9)	C(10)	1.506(5)
C(10)	C(14)	1.509(6)
C(10)	C(1)	1.344(6)
C(8)	O(8)	1.456(4)
O(8)	C(8A)	1.328(4)
C(8A)	O(8A)	1.200(6)
C(8A)	C(8M)	1.488(6)

FIGURE 1. ^{1}HNMR spectrum of Heliangolidin

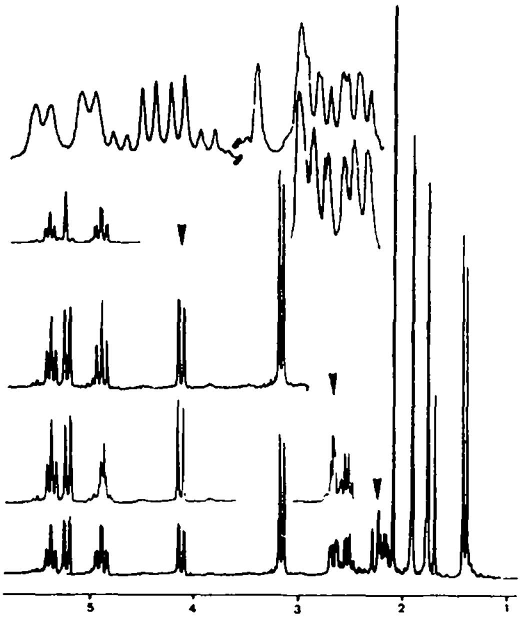


FIGURE 2. ^{1}H-^{13}CNMR correlated spectrum of Heliangolidin

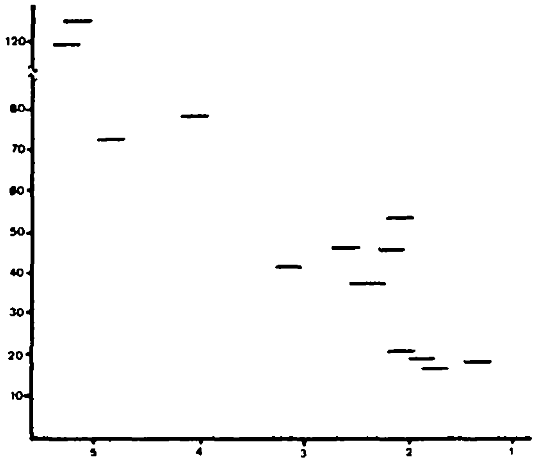


FIGURE 3. Stereoscopic view of Heliangolidin

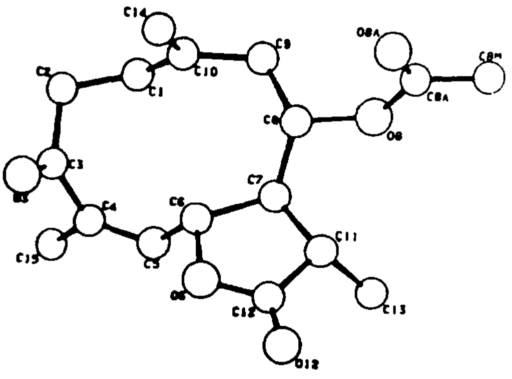


TABLE 4. Bond Angles (°) for Heliangolidin

Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle
C(1)	C(2)	C(3)	107.4(3)	C(6)	C(7)	C(11)	104.5(3)
C(2)	C(3)	O(3)	123.4(4)	C(6)	C(7)	C(8)	115.4(3)
C(2)	C(3)	C(4)	115.2(4)	C(7)	C(6)	O(6)	105.7(3)
O(3)	C(3)	C(4)	121.3(4)	C(11)	C(7)	C(8)	110.3(3)
C(3)	C(4)	C(15)	114.8(4)	C(7)	C(8)	C(9)	117.0(3)
C(3)	C(4)	C(5)	123.8(4)	C(8)	C(9)	C(10)	113.3(3)
C(15)	C(4)	C(5)	120.9(4)	C(9)	C(10)	C(14)	117.1(4)
C(4)	C(5)	C(6)	123.5(4)	C(9)	C(10)	C(1)	119.7(4)
C(5)	C(6)	C(7)	113.3(3)	C(14)	C(10)	C(1)	123.1(4)
C(5)	C(6)	O(6)	106.1(3)	C(7)	C(8)	O(8)	104.6(3)
C(6)	O(6)	C(12)	112.8(3)	C(8)	O(8)	C(8A)	119.1(3)
O(6)	C(12)	O(12)	121.6(4)	O(8A)	C(8A)	C(8M)	112.6(3)
O(12)	C(12)	C(11)	126.9(4)	C(8M)	C(8A)	O(8A)	125.1(4)
O(6)	C(12)	C(11)	111.5(3)	O(8)	C(8A)	O(8A)	122.3(4)
C(12)	C(11)	C(13)	110.3(4)	O(8)	C(8)	C(9)	106.2(3)
C(12)	C(11)	C(7)	105.6(3)	C(10)	C(1)	C(2)	125.6(4)
C(13)	C(11)	C(7)	114.4(4)				

TABLE 5. Experimental and Statistical Data for Heliangolidin

a(Å)	9.727(6)	T(°K)	294
b	10.229(5)	F(000)	656
c	16.772(9)	Max. 2Θ(°)	23.5
V(Å^3)	1668.8(7)	Unique Reflections	1474
Z	4	I>2.5σ(I)	1163
Crystal Form	orthorhombic	L.S. Parameters	266
Space Group	P $2_12_12_1$	R	0.052
		Rw	0.054
Dx (Mg M^{-3})	1.219	Max. Residual (e Å^{-3})	0.24
M.W.	306.4	Min. Residual (e Å^{-3})	-0.25
μ (MoKα)	0.833 cm^{-1}		

TABLE 6. Final Atomic Coordinates for the Non-hydrogen Atoms (x10^4) and Equivalent Isotropic Temperature Factors (x10^3) for Heliangolidin

Atom	X	Y	Z	B^*_{eq}(Å^2)	Atom	X	Y	Z	B^*_{eq}(Å^2)
O(3)	11603(4)	-2605(4)	5053(2)	7.0(2)	C(7)	8344(4)	192(3)	3697(2)	3.5(1)
O(6)	8670(3)	128(3)	5125(2)	4.9(2)	C(8)	7684(4)	-844(4)	3163(2)	3.8(1)
O(8)	6757(3)	-113(2)	2648(1)	4.1(1)	C(8A)	5548(4)	-631(3)	2458(2)	4.1(1)
O(8A)	5177(4)	-1699(3)	2712(3)	8.1(2)	C(8M)	4736(4)	218(4)	1912(3)	4.9(2)
O(12)	9913(4)	1327(4)	5551(2)	8.0(2)	C(9)	8647(4)	-1613(4)	2607(2)	4.6(2)
C(1)	10981(4)	-2137(4)	3082(2)	4.5(1)	C(10)	9647(4)	-2475(4)	3046(2)	4.3(1)
C(2)	12016(4)	-2698(4)	3639(3)	5.1(2)	C(11)	7226(4)	987(4)	4133(2)	5.2(2)
C(3)	11825(4)	-2025(4)	4443(2)	4.9(2)	C(12)	7544(4)	853(4)	5004(2)	4.8(2)
C(4)	11856(4)	-553(4)	4420(3)	5.0(2)	C(13)	7170(7)	2409(5)	3901(3)	11.1(3)
C(5)	10733(4)	192(4)	4359(2)	4.6(2)	C(14)	9066(4)	-3654(4)	3468(3)	5.6(2)
C(6)	9281(4)	-348(4)	4382(2)	3.8(1)	C(15)	13294(5)	45(5)	4352(3)	6.6(2)

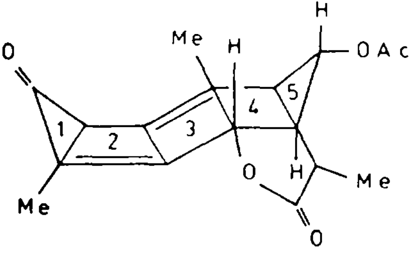
*Calculated from the refined anisotropic thermal parameters

$$B_{eq} = 8\pi^2 U_{eq} = \frac{8}{3}\pi^2 \Sigma_i \Sigma_j U_{ij} a_i^* a_j^* \underline{a}_i \underline{a}_j$$

The cyclodecadiene ring is described by five roughly planar regions:

Plane (1): C(2), C(3), C(4);
Plane (2): C(1), C(2), C(4), C(5)
(r.m.s.d: 0.113 and maximum deviation 0.14Å);
Plane (3): C(1), C(5), C(6), C(10)
(r.m.s.d: 0.045 and maximum deviation 0.05Å);
Plane (4): C(6), C(7), C(9), C(10)
(r.m.s.d: 0.009 and maximum deviation 0.01Å) and
Plane (5): C(7), C(8), C(9).

FIGURE 4.



The dihedral angle between planes (1) and (2) is 57.5° and that between planes (2) and (3) is 52.0°, which define a boat region; the dihedral angle between planes (3) and (4) is 63.6° and that between planes (4) and (5) is 58.8°, which define a chair region (Fig. 4). Therefore, the cyclodecadiene ring adopts a chair-boat conformation comparable to that found in eupaformonin[9] and dihydroheliangin[10].

Likewise, as in these germacranolide sesquiterpenes, the value of the torsion angle of the *cis* double bond (C(3)-C(4)-C(5)-C(6): 5.7°) is lower than that of the *trans* double bond (C(9)-C(10)-C(1)-C(2): 164.8°) in agreement with the more strained character of the latter. On the other hand, the C(2)-C(1)-C(10)-C(14) torsion angle (-11.6°) is higher than that found in dihydroheliangin[10] (-7°).

The γ-lactone ring adopts a planar conformation (mean plane: (C(6)-C(7)-C(11)-C(12)-O(6), r.m.s.d: 0.004, maximum deviation: 0.005Å), the O(12) atom also lying in this plane. Similarly, the acetate ester group is also planar (r.m.s.d. 0.001 and maximum deviation: 0.002A) forming an angle of 78.8° with the mean plane. The observed mean length distances are within the range of the accepted values: (C(Sp^3)-C(Sp^3) 1.536(21), C(Sp^3)-C(Sp^2) 1.508(16), C(Sp^2)-C(Sp^2) 1.507, C=C 1.340(6), C(Sp^3)-O(R) 1.460(6), C(Sp^2)-O(R) 1.333(7) and C=O 1.203(3).

The shortest intermolecular contacts are O(8A)...C(8M)^{i} = 3.249Å (i=1.-x,0.5+y,0.5-z), O(6)...O(3)^{ii}= 3.284Å (ii=-0.5+x,0.5-y,1.-z) and C(8M)...O(6)^{iii}= 3.392Å (iii=1.5-x,-y,-0.5+z).

EXPERIMENTAL

Melting points were measured on a Kofler hot stage apparatus and are corrected, U.V. spectra were obtained in ethanolic solution with a Perkin-Elmer 550S spectrometer. Optical measurements were determined in a Perkin-Elmer 141 polarimeter. Infrared spectra were recorded on a Perkin-Elmer 681 spectrometer in solution using $CHCl_3$ as solvent. Low-resolution and high-resolution mass spectra were recorded on a VG Micromass ZAB-2F spectrometer. ^{1}HNMR and ^{13}CNMR spectra were made at 200 and 50.32 MHz, respectively, on a Bruker WP-200 SY spectrometer, using the solvent deuterium signal to field-frequency lock the spectrometer. The heteronuclear ^{13}C-^{1}H shift correlated 2-D NMR was performed using a Bruker WP-200 SY spectrometer upgraded with an Aspect-2000 computer. The applied pulse sequence was

$$(\pi/2,\ ^1H)-(\tau_1/2)-(\pi,\ ^{13}C)-(\tau_1/2)-\Delta_1\ (\pi/2,\ ^1H;\pi/2,\ ^{13}C)-\Delta_2$$

acquisition with Δ_1 = 4 ms and Δ_2=2 ms. The spectral width was in F_1= 1101.2 Hz (5.4 ppm), in F_2 = 7042.2 Hz (139.9 ppm); the number of data points in F_2 was 4000 and 70 increments were recorded.

Isolation of Heliangolidine from *Artemisia canariensis*. Air dried aerial parts of *A. canariensis* Lees (10 kg) collected in January 1984 in Mesa Mota (Tenerife, Spain) were finely ground and extracted with boiling water under pressure for 6 h. The aqueous solution was then continuously extracted with $CHCl_3$. Evaporation of the $CHCl_3$ extract furnished a residue (33.3 g) which was chromatographed over 250 g of silica gel, eluting with hexane-ethyl acetate and collecting 50 ml fractions as follows: 400 ml 4:1, 400 ml 2:1, 1000 ml 4:3, 600 ml 1:1, 400 ml 1:2 and 200 ml 0:1. The combined 4:3 fractions afforded crude heliangolidin (7) (400 mg) which was purified by column chromatography over 38.6 g of silica gel eluting with a 3:2 hexane-ethyl acetate mixture and recrystallization from ethyl acetate gave 227 mg of pure 7: m.p. 187-189°C; $[\alpha]_D$ = + 216.5° (c 0.194, $CHCl_3$); UV λ_{max}(EtOH) 293 nm (ϵ 175); IR(KBr) 1765, 1735, 1695 cm^{-1}; MS, m/z (relative percent) 306 (M^+, 2.4), 264 (M^+-42, 1.73), 246 (M^+-60, 1.22), 209 (1.93), 194 (3.66), 173 (3.91), 167 (32.77); Anal. calcd. for $C_{17}H_{22}O_5$ C 66.65%, H 7.24%, and found C 66.48%, H 6.98%.

X-Ray Analysis of Heliangolidin. Single crystals of 7 were prepared by slow crystallization from ethyl acetate solutions. A single crystal of dimensions 0.23 x 0.32 x 0.16 mm, cut from an irregular crystal of 5 x 3 x 1 mm, was mounted on an Enraf-Nonius CAD-4F automated diffractometer.

Cell parameters were derived from the setting angles of 25 reflections with $4^\circ < \theta < 11^\circ$. Intensity data were collected using the ω-2θ scan technique with graphite monochromatized MoKα radiation. Intensities were not corrected for absorption or extinction $\theta_{max} = 23.5^\circ$, h = 0-10, k: 0-11, l:0-18. Three reference reflections were measured every hour and revealed no decay (variation<1%). Lorentz and polarization corrections were applied to the 1474 unique reflections and the 1163 with $I > 2.5\sigma(I)$ were used in the refinement of the structure. The direct methods program[11] MULTAN 11/82 was used to solve the structure and the refinement on F was carried out by full matrix least squares[12]. Refined parameters included atomic positions of all atoms and anisotropic temperature factors for non-hydrogen atoms. The hydrogen atoms were refined with common isotropic temperature factors and its positions were determined from difference Fourier synthesis except the methyl hydrogens which were calculated. The function minimized in the refinement was $\Sigma w(||F_o|-|F_c||)^2$ where $w = 1/(\sigma^2(F)+0.009625F^2)$, $\sigma(F)$ was derived from counting statistics.

Final R and Rw were 0.052 and 0.054, respectively. Parameters refined n= 266, $(\Delta/\sigma)_{max} = 0.25$. Maximum and minimum heights in final difference Fourier synthesis were 0.24 and -0.25 eÅ^{-3}. Additional computer programs used were XANADU[13] and PLUTO[14]. Table 5 presents a summary of experimental and statistical data for 7. Final atomic positions and equivalent isotropic thermal parameters with their estimated standard deviations (e.s.d.) are listed in Table 6.

ACKNOWLEDGMENTS

Financial support from Comisión Asesora de Investigación Científica y Técnica is gratefully acknowledged. L. Eguren thanks the Asociación de Investigación y Especialización sobre Temas Iberoamericanos (AIETI) for a fellowship and E. Molins, C.S.I.C. for a predoctoral fellowship.

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